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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/758,007	01/10/2001	Leonard I. Zon	701039-50920	8096

7590 08/20/2003

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	15

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/758,007	ZON ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the corresp ndence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *1-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment and remarks filed 5/21/03 has been entered as paper #14. Claims 1-29 are pending, claims 18, 25, and 29 have been amended, claims 1-17 have been withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions. Claims 18-29 are under current examination.

Unless otherwise indicated, previous rejections that have been rendered moot in view of the amendment to pending claims will not be reiterated. The arguments in paper #14 would be addressed to the extent that they apply to current rejection.

This application contains claims (1-17) drawn to an invention nonelected with traverse in Paper No. 11. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18-29 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In paper#14, applicants indicated that claim 18 has been amended to recite "identifies" instead of "indicates", and the support for the amendment could be found in page 3 of the specification. Applicants also indicates that the positional cloning is not a necessity for identifying a gene.

The argument has been fully considered but found not persuasive. It is true that the method of identifying a gene does not necessarily use positional cloning, the Office cites it as an example, rather than a requirement. However, the paragraph pointed out by the applicants does not support the amendment of claim 18. The last paragraph in page 3 spanning to page 4 only teaches that abnormal cell proliferation in the embryos "**indicate**" that specific strain harbors a gene involved in cell proliferation, this part of the specification does not teach how the abnormal cell proliferation *identifies* a gene. The paragraph before the last one in page 3 only teaches steps (a) to (d) of the claimed method. Accordingly, Claims 18, 19, and 21-29 remain rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted step is: how an abnormal gene is identified so that the body of the claim would clearly relate back to the preamble.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 18-21, 23, 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH) in view of *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533) and *Alexander et al* (Dev Genet 1998;22:288-299).

In paper #14, applicants argue that nothing in Spitsbergen teaches or suggests that mutated fish can be used in to identify novel genes associated with carcinogenesis a screening method including a carcinogenesis screen, nowhere in Driver is there even a mention of use of the fish in identifying mutations using a cell proliferation marker, Cheng describes a comparison of two-generation zebrafish screens involved in development, not carcinogenesis, or using a marker to identify mutants in fish embryo; and Alexander does not teach or suggest the use of zebrafish to identify genes with cell proliferation defects. Therefore, the references even in combination do not teach all the steps of the claimed method, and all the secondary references describe use of a zebrafish for studying developmental process, not genes associated with

carcinogenesis, and since the two belong to different field of research, one skilled in the art would not have been motivated to combine all the references.

The arguments are fully considered, but they are not persuasive for reasons of record and following.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In the instant case, *Spitsbergen et al* teach the feasibility of using zebrafish for studying carcinogen known to causing carcinogenesis in humans, i.e. whether zebrafish would respond to a human carcinogen in a way that correlates to human cancer, and concluded, "ZEBRAFISH OFFER A COST-EFFECTIVE, RELATIVELY RAPID SYSTEM IN WHICH TO ADDRESS QUESTIONS REGARDING CELLULAR AND MOLECULAR MECHANISMS IN CARCINOGENESIS" (last paragraph, page 10). Here, it is obvious to one of ordinary skill in the art, that the recited "molecular mechanism" implies changes at the *gene* level when responding to carcinogen. Therefore, *Spitsbergen et al* are aware of, investigating, and suggesting the feasibility of using zebrafish for gene discovery associated with carcinogenesis of certain chemical mutagen, they teach exposing the fish to different dose of a mutagen with different exposure routes (step a or f) and observing the tumor formation in zebrafishes (step g). Thus, contrary to applicants conclusion, *Spitsbergen et al* do teach steps (a), (g), & (f) of instantly claimed method.

Driever reference is relied upon as a showing for the general state of the art using zebrafish for genetic screening. Driever reference repeatedly teaches using zebrafish for screening mutations (see particularly the Section spanning pages 1789-1792). Although the focus of the *Driever* reference is on the embryo development, *Driever et al* are certainly aware of using zebrafish for studying gene linkage to common disease, because they state, "OF COURSE, ITS CONTRIBUTIONS CAN ONLY BE ENHANCED, ONCE THE GENES ARE CLONED, ...BY ASSESSMENT OF LINKAGE TO COMMON DISORDERS" (last sentence of the article), cancer is certainly a well known common disorder. Moreover, *Driever et al* also teach the principle of using "ASSAYS OF CELL POPULATIONS WHICH ARE DISPERSED OR DEFINED ONLY BIOCHEMICALLY" for zebrafish screening assay as one of the future directions (starting at line 4 of the last section). Even though a specific cell proliferation marker is not mentioned, it is within the knowledge of the skill regarding the tools (markers) to be used in a cell population assay. Thus, contrary to applicants conclusion, *Driever et al* do teach steps (e) & (g) of instantly claimed method. The outline reviewed by *Driever et al* illustrated the state of the art in using zebrafish for investigating genes important for vertebrate development and readily applicable for investigating mutagens and carcinogenesis.

Cheng et al and *Alexander et al* references are relied upon for details of using zebrafish in uniparental and two-generation screening ((steps (b)-(d), (f) & (g) of instantly claimed method). Although the focus of the two references are developmental defects, they certainly teach that the approach has much broader utility in gene discovery. For example, *Chang et al* teach, "THE INCREASINGLY POWERFUL GENETIC AND

EXPERIMENTAL TOOLS AVAILABLE FOR WORK WITH ZEBRAFISH CAN BE USED TO ADDRESS A BROAD RANGE OF QUESTIONS IN VERTEBRATE BIOLOGY" (abstract), and "IT IS ALSO IMPORTANT TO POINT OUT THAT THE EXPERIMENTAL FEATURES THAT MAKE THE ZEBRAFISH SO USEFUL IN DISSECTING THE MYSTERIES OF THE DEVELOPMENT CAN BE APPLIED TO THE ELUCIDATION OF OTHER SIGNIFICANT PROBLEMS IN VERTEBRATE BIOLOGY" (last sentence of the article). *Cheng et al* specifically listed the mutagens that could be used in **mutagenesis** study, which are the same type as instantly claimed, i.e. gamma-ray, and *N*-nitroso compounds. In fact, the mutagen used by *Alexander et al* and taught by *Cheng et al* for studying developmental defect of zebrafish is the same type of compound as used by *Spitsbergen* for studying **carcinogenesis** in zebrafish, i.e. *N*-nitroso compounds. Obviously, the means for studying the mutagenesis and carcinogenesis are overlapping, and at the time of instant filing date, many common approaches and tools have been widely used for studies in different research fields.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Driever et al, Cheng et al, Alexander et al* with the method taught by *Spitsbergen et al* for screening genes involved in carcinogenesis with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the modified method could expedite the process and discover the dominant and recessive genes as well as influential genes involved in tumorigenesis. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Applicants are reminded that the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Accordingly, for reasons of record and analysis set forth foregoing, the rejection stands.

Claims 18-24, and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH), *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533), and *Alexander et al* (Dev Genet 1998;22:288-299) as applied to claims 18-21, 23, 29 above, and further in view of *Epstein et al* (US 5,756,476).

In paper #14, applicants argue that Epstein merely teaches antisense oligos as cell proliferation markers but does not in any way teach or suggest use of such probes in a zebrafish screening. Applicants also allege that the Examiner has not provide indication that one of ordinary skill in the art, without knowledge of the claimed invention, would piece together the teachings of five references to result in the claimed invention.

The argument has been carefully considered but found not persuasive.

The general analysis for combining *Spitsbergen et al*, *Driever et al, Cheng et al*, and *Alexander et al* has been provided in the above section, will not reiterated here.

Specifically related to this rejection is whether the skilled in the art knows to use a gene probe in zebrafish screening. To this end, as indicated previously, *Driever et al* teach using gene probe and cell population assays in zebrafish screening (§Future directions). *Cheng et al* teach in situ hybridization in fish embryo screening (table, page 526), and *Alexander et al* use in situ hybridization (probes), and immunofluorescence for fish embryo screening. The *Epstein* reference is relied upon as a showing that the particular markers, their association with cell proliferation and tumor formation are known in the art and have been used for cancer diagnosis.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Spitsbergen et al, Driever et al, Cheng et al, Alexander et al* with the method taught by *Epstein et al* using PCNA and/or cyclin-b1 for haploid embryo screening with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because these markers are known in the art to be associated with proliferation defect and tumor formation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

The following rejection is necessitated in view of the amendment of claim 25.

Claim 25 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH), *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533), and *Alexander et*

al (Dev Genet 1998;22:288-299) as applied to claims 18-21, 23, 29 above, and further in view of *Vogelstein et al* (US 6,511,818).

The amended claim 25 is specifically directed to using flow cytometry detecting dye staining for DNA content indicating a problem in cell proliferation.

The combined teachings of *Spitsbergen et al*, *Driever et al, Cheng et al*, and *Alexander et al* do not specify the particular method.

However, before the effective filing date of instant application, *Vogelstein et al* teach using flow cytometry assay for DNA content, its association with cell proliferation cycle and using such for cancer drug screening (see particularly, column 1, lines 37-46, and column 3, lines 24-45).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Spitsbergen et al, Driever et al, Cheng et al*, *Alexander et al* with the method taught by *Vogelstein et al* using DNA content flow cytometry for haploid embryo screening with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the method is known in the art for assessing cell proliferation defect related to cancer. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

In paper #14, applicants argue that *Shyjan* merely teaches using cell proliferation markers in the flow cytometric assay but does not in any way teach or suggest use of such assay in a zebrafish screening. Applicants also allege that the Examiner has not provide indication that one of ordinary skill in the art, without knowledge of the claimed

invention, would piece together the teachings of five references to result in the claimed invention, and the only way to achieve such result is through impermissible hindsight obviousness.

The argument has been carefully considered but found not persuasive.

The general analysis for combining *Spitsbergen et al*, *Driever et al, Cheng et al*, and *Alexander et al* has been provided in the above section, will not reiterated here. Specifically related to this rejection is whether the skilled in the art knows to use the flow cytometry assay in zebrafish screening. To this end, *Driever et al* teach using biochemical cell population assays in zebrafish screening (§Future directions). *Cheng et al* teach in situ hybridization in the embryo screening (table, page 526), and *Alexander et al* use in situ hybridization (probes), and immunofluorescence for the embryo screening. The previous Shyjan reference or current *Vogelstein* reference is relied upon as a showing that the particular assays, their association with cell proliferation and cancer screening are known in the art.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, all the references cited are prior art, the reconstruction takes

into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, thus, it is proper. Accordingly, the rejection stands.

Claims 18-21, 23, 26, 27, and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH), *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533), and *Alexander et al* (Dev Genet 1998;22:288-299) as applied to claims 18-21, 23, 29 above, and further in view of *O'Reilly et al* (US 5,854,205).

In paper #14, applicants argue that *O'Reily* merely teaches TUNEL for identifying cell proliferation defect but does not in any way teach or suggest use of such assay in a zebrafish screening. Applicants also allege that the Examiner has not provide indication that one of ordinary skill in the art, without knowledge of the claimed invention, would piece together the teachings of five references to result in the claimed invention, and the only way to achieve such result is through impermissible hindsight obviousness.

The argument has been carefully considered but found not persuasive.

The general analysis for combining *Spitsbergen et al*, *Driever et al, Cheng et al*, and *Alexander et al* and other arguments which have been addressed in the above sections will not be reiterated. Specifically related to this rejection is whether the skilled in the art knows to use a TUNNEL assay in the zebrafish screening. To this end, *Driever et al* teach using biochemical cell population assays in zebrafish screening (§Future directions). *Cheng et al* teach in situ hybridization in the embryo screening (table, page

526), and *Alexander et al* use in situ hybridization (probes), and immunofluorescence for the embryo screening. The O'Riley reference is relied upon as a showing that the particular assay, its association with cell proliferation and cancer screening are known in the art.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Spitsbergen et al, Driever et al, Cheng et al, Alexander et al* with the method taught by *O'Reilly et al* using apoptotic markers for haploid embryo screening with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because these markers are known in the art to be associated with proliferation defect and tumor formation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 18-21, 23, 28, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Spitsbergen et al* (Toxicol Pathol 2000;28:716-725, IDS/CH), *Driever et al* (J Clin Invest 1996;97:1788-94), *Cheng et al* (Biochem Cell Biol 1997;75:525-533), and *Alexander et al* (Dev Genet 1998;22:288-299) as applied to claims 18-21, 23, 29 above, and further in view of *Li et al* (US 5,679,523).

In paper #14, applicants argue that *Li* only teaches BrdU stain for identifying cell proliferation defect but does not overcome the deficiencies in other four references. Applicants also allege that the Examiner has not provide indication that one of ordinary skill in the art, without knowledge of the claimed invention, would piece together the

teachings of five references to result in the claimed invention, and the only way to achieve such result is through impermissible hindsight obviousness.

The argument has been carefully considered but found not persuasive.

The general analysis for combining *Spitsbergen et al*, *Driever et al, Cheng et al*, and *Alexander et al* and other arguments which have been addressed in the above sections will not be reiterated here. Specifically related to this rejection is whether the skilled in the art knows to use a BrdU assay in the zebrafish screening. To this end, *Driever et al* teach using biochemical cell population assays in zebrafish screening (§Future directions). *Cheng et al* teach in situ hybridization in the embryo screening (table, page 526), and *Alexander et al* use in situ hybridization (probes), and immunofluorescence for the embryo screening. The Li reference is relied upon as a showing that the particular assay, its association with cell proliferation and cancer screening are known in the art.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the methods taught by *Spitsbergen et al, Driever et al, Cheng et al*, *Alexander et al* with the method taught by *Li et al* using BrdU assay in haploid embryo screening with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the marker is known in the art to be associated with proliferation defect and tumor formation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
August 8, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER